have been picked up with early symptoms and been treated, when the clinical picture becomes distorted. There is no direct correlation between the cholinesterase depression in the blood and signs or symptoms; in general 85% or more of the red cell cholinesterase may be inhibited before there are any overt indications of poisoning. At a slightly lower degree of inhibition some men develop a general malaise and desire to stay quiet and rest, but this malaise can be overcome and men poisoned to this extent can still remain active and carry out normal routines. At about 90% depression gastro-intestinal symptoms may intervene. The relation between the dose required to give 50% cholinesterase inhibition in the blood and the LD50 varies with different agents and with different species. It may be as little as 1: 4 or as great as 1:16, but in no case does death occur until there is virtually complete inhibition of the blood cholinesterase and in general there is no cause for anxiety if the blood cholinesterase level does not fall to less than 25% of its normal value. Nevertheless spontaneous reactivation of the blood cholinesterase does occur and there are recorded cases of proved death by anticholinesterase poisoning, e.g. by Parathion, in which the cholinesterase level in the blood after death has been quite high; this suggests that brain cholinesterase may be reactivated more slowly than blood cholinesterase. There is also some suggestion, however, that with repeated minor exposures symptoms may occur at slightly higher cholinesterase levels (Holmes & Gaon 1956).

The cause of death in man is anoxia, but in warm climates there is an additional hazard as the heat regulating centre may also be put out of action and there may be alarming rises in the body temperature, to heat stroke levels. Artificial respiration may not therefore be enough to keep a casualty alive; he may die, or suffer irreparable damage, from hyperpyrexia.

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The Use of Organophosphorus Compounds in Veterinary Medicine

by S B Kendall PhD MRCVS (*Weybridge*)

At present the number of organophosphorus compounds in veterinary medicine is limited but there is every reason to believe that a wide range will become available. These compounds vary greatly in physical and biological properties, and especially in stability, solubility and mode of action *in vivo* (Spencer & O'Brien 1957). Some are contact poisons while others act systemically after absorption from gut, dermis or mucous membrane, in some cases after alteration in the body.

Available Organophosphorus Compounds

Among the compounds used in veterinary medicine are:

(1) *Neguvon* (Bayer 13/59; Dipterex Chlorophos)
0,0, dimethyl-l-hydroxy-2-trichlorethyl phosphonate

(2) *Ruelene:* (Dowco 132)
0-(4 tert. butyl 2 chlorophenyl)-0-methyl methylphosphoramidate

(3) *Asuntol:* (Bayer 21/199: Muscatox Coumaphos: Co-Ral)
0,0-diethyl 0-3 chloro-4-methyl umbelliferyl phosphorothioate

(4) *Delnav:* (Bercotox)
2 : 3-dioxane dithiol-S-bis (0,0-diethyl dithiophosphonate)

(5) *Diazinon:*
0,0 diethyl 0-(2-isopropyl-4-methyl-6-pyrimidyl) phosphorothioate

(6) *Etrolene:* (Dow ET-57, Ronnel, Trolene)
0,0 dimethyl 0-2, 4, 5-trichlorphenyl phosphorothioate

For convenience these substances are referred to below by their proprietary names.

Acaricides

Organophosphorus compounds have been used in several countries for the control of ticks but a small experiment carried out at Weybridge by my colleague Mr W N Beesley, has not confirmed the reports of the efficiency of Etrolene against sheep scab mite (*Psoroptes communis ovis*).

As acaricides, the organophosphorus compounds have the advantage of being stable in dip tanks and some have a long residual effect when on the hair or skin of cattle. Larvæ of boophilus were killed twenty-eight days after a spray application of Asuntol (Harbour 1960, personal communication). Neguvon, by contrast, although its effect on ticks may be more rapid, has little residual effect. Wood *et al.* (1960) showed that 0·1% Delnav gave five to six weeks protection against *Ixodes ricinus* (the only economically important tick in Britain). As the major period of activity of *I. ricinus* is for a few weeks only in March–May, a Delnav dip in late March or early May just before lambing should substantially protect against serious infestation.

Delnav has been successfully used in Australia, the U.S.A. and in East and South Africa for tick control, and in South Africa Delnav has been found effective against strains of boophilus resistant to Toxaphene and to chlorinated hydrocarbons.

As dips the organophosphorus compounds have the disadvantage that they allow the growth of weeds, bacteria, protozoa and fungi and hence may encourage the development of mycotic conditions in the fleece.

Insecticides

In Australia, Diazinon has been widely used for plunge dipping and shower spraying in the control of *Lucilia cuprina* which has become resistant to dieldrin, and Delnav has been used similarly against blowflies. At Weybridge sheep sprayed with Asuntol resisted artificial infection with *Lucilia sericata* for up to three months.

Considerable information is available about the use of systemic organophosphorus compounds for the control of warble-flies in cattle. Here the aim is that the insecticide should act against the larvæ of hypoderma during their migration through the body (Adkins 1957, MacGregor & Bushland 1957). Etrolene has been found to be effective when given orally as a bolus or as a suspension in water, and free-choice feeding to cattle has been suggested by Kohler *et al.* (1959) and Rich (1960). Etrolene does not appear to be effective as a systemic insecticide when applied to intact skin.

Co-Ral also is used for the control of warble-flies (Smith & Richards 1954, Roth & Eddy 1955). Neguvon is too toxic for general oral administration, but Rosenberger (1959) has demonstrated that dermal application is both safe and effective.

While none of these organophosphorus compounds seems to be entirely effective in the control of the migrating larvæ of hypoderma they undoubtedly represent a major advance towards control of the parasite. A number of factors, however, make effective control of the warble-fly difficult. Not the least is the reluctance of the farmer to expend much time or money on measures of control. The organophosphorus compounds are relatively expensive and their use for warble-fly control would be considerably encouraged if they were shown to exert also an anthelmintic effect (*see* Swanson & Collier 1960).

Anthelmintics

Several of the organophosphorus compounds have been shown to have anthelmintic activity. Neguvon, for example, is very effective against adult *Ostertagia ostertagi* and *T. axei* (Banks & Michel 1960, Dunsmore 1960) but there is no apparent effect against the immature worms of ostertagia. Ruelene has been found to be effective in varying extents against adult ostertagia, nematodirus, strongyloides and *T. axei* (Douglas & Baker 1959). Alicata (1960) found cooperia very susceptible. Asuntol was found effective against hæmonchus, cooperia, *T. axei* and also against the larvæ of ostertagia by Kingsbury (1960, personal communication).

Etrolene is effective against hæmonchus and cooperia and to a less extent against strongyloides (Gordon 1958, Riek 1958, Riek & Keith 1959).

The Mode of Action of the Compounds

Any detailed consideration of the mode of action of these compounds is beyond the scope of this paper but a few general points of interest may be mentioned.

Acaricides such as Asuntol appear to act solely as contact poisons. The effect on fed adult ticks is very much slower than that on the immature forms. Adults may take two to three days to drop to the ground. There appears to be no effect at all if the active principle of Asuntol is given orally to the infested animal. By contrast the organophosphorus compounds used for warble-fly control clearly act systemically. In general it can be assumed that the insecticidal effect is due to the inhibition of cholinesterase activity, although there is evidence (Lord & Potter 1954, Fukuto 1957) that not all species of insects susceptible to organophosphorus compounds possess esterases capable of being inhibited and that in some cases a high insecticidal action is found without a correspondingly high anticholinesterase activity.

The fact that some compounds, such as Asuntol, are effective against the warble-fly grub when applied dermally to cattle but ineffective when given orally has led to many studies of the metabolism of organophosphorus compounds. The mammalian liver appears to be the organ mainly concerned (O'Brien & Wolfe 1959). In some mammals (e.g. the mouse) the compound is 'activated' i.e. converted to a potent anticholinesterase analogue and there is no degrading, but in the ox degradation is greater than activation. In hypoderma which is particularly susceptible to organophosphorus poisoning, there is an activating but no degrading system. These studies help to explain both the selective toxicity of Asuntol and the reason why only dermal treatment controls the grubs. With oral dosing the liver inactivates the drug before it reaches the larva.

Toxicity

Organophosphorus compounds must be regarded as potentially toxic to the host as well as the parasite and it is necessary to consider possible deleterious effects not only on domestic animals but also on the human population that handles the compounds and that consumes meat and milk from treated animals.

The signs of toxicity in domestic animals have been described by Dr Ladell (p. 405) and by Jolly

(1957) who gives an account of poisoning in cattle after spraying with a thiophosphate derivative for tick control. Some animals collapsed and died within thirty minutes of the onset of symptoms. Those which survived were recumbent for five to six hours but then recovered.

In some early experiments at Weybridge Etrolene at dosages of about 250 mg/kg (two and a half times those recommended for ordinary use) gave rise to characteristic signs of toxicity in young calves which recovered in about forty-eight hours. Dramatic but transient poisoning has been observed at the recommended dosage levels (110 mg/kg) under field conditions.

Toxicity may vary according to the route by which a compound is administered. Thus Neguvon given percutaneously is reported to be much less toxic than when given orally although it retains its parasiticidal efficacy (Rosenberger 1959). Holmstedt (1959) demonstrated that percutaneous absorption of organophosphorus compounds was a relatively slow process and that enzymes in the skin were capable of hydrolysing the compounds before they reached the blood stream. Minor skin injuries may reduce the resistance to absorption and result in a considerable increase in toxicity.

It seems likely that the different behaviour of some compounds according to the route of administration may be explained partly in terms of liver metabolism and partly as the result of skin hydrolysis.

Toxicity to Man

The hazards associated with the handling of toxic substances are usually predictable and can be guarded against. The possible hazard to the population at large as the result of consuming toxic residues in food must not be exaggerated but nevertheless needs consideration in view of the increasing use of phosphorus compounds in different branches of agriculture. The persistence of these compounds in animal tissues is likely to vary considerably. Neguvon, for example, which is water soluble appears to be rapidly destroyed in the mammalian body and little is detectable after about twelve hours (Harbour 1960, personal communication). Each case will need to be considered on its merit. In Britain the use of compounds for the control of warble-flies is restricted by voluntary agreement with the manufacturers.

Conclusion

From the practical point of view the development of the organophosphorus compounds has already resulted in some worthwhile advances and there is little doubt that other compounds, perhaps with a broader spectrum of activity against the parasites and a lower toxicity to their hosts will be forthcoming. A very great field for further research remains, particularly along the lines suggested by the observation that both toxicity and parasiticidal activity may vary very markedly not only as between related animal species but also according to the route by which the organophosphorus compounds are administered.

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